



TITLE:

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AUTHOR(S):

Uno, Takuya; Inokuma, Tsubasa; Takemoto, Yoshiji

CITATION:

Uno, Takuya ...[et al.]. NHC-catalyzed thioesterification of aldehydes by external redox activation.. Chemical communications 2012, 48(13): 1901-1903

ISSUE DATE:

2012-02-11

URL:

<http://hdl.handle.net/2433/166620>

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

NHC-catalyzed Thioesterification of Aldehydes by External Redox Activation

Takuya Uno, Tsubasa Inokuma and Yoshiji Takemoto*

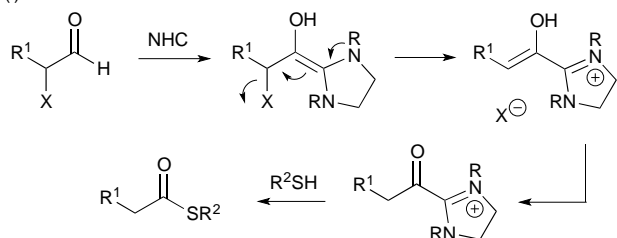
Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

DOI: 10.1039/b000000x

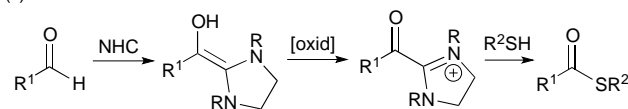
The NHC-catalyzed thioesterification of aromatic or aliphatic aldehydes with a range of thiols was developed in the presence of a stoichiometric amount of an organic oxidant. Among the oxidants examined, phenazine was shown to give the best results in terms of chemical yield and compatibility with thiols.

Thioesters are important compounds from both synthetic and biological perspectives. They have frequently been used as synthetic intermediates for acyl transfer reactions,¹ including native chemical ligation,² functional group transformations³ into ketone and aldehyde, and the formation of carbon-carbon bonds⁴ such as in the aldol and Michael reactions. In nature, acetyl-CoA, a biologically important thioester, plays a pivotal role in fatty acid and polyketide biosynthesis.⁵ To synthesize such versatile thioesters, various methods have been developed: (1) condensation⁶ of carboxylic acid and thiol with dehydrating reagents, (2) transthioesterification⁷ of active carboxylic acid derivatives with thiol, (3) palladium-catalyzed thiocarbonylation⁸ of iodoarenes and thiol with carbon monoxide, and (4) radical-mediated coupling⁹ of aldehyde with disulfide or thiol. However, the discovery of efficient catalytic methods for thioesters remains an important synthetic challenge in organic chemistry.

(i) Internal redox reaction



(ii) external redox reaction

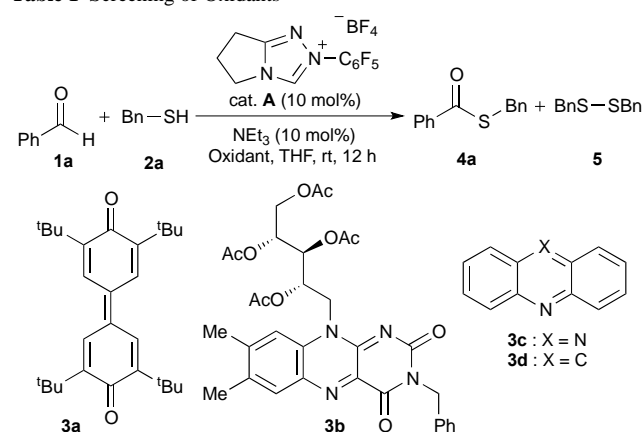


Scheme 1 NHC-Catalyzed thioesterification of aldehydes by the internal and external redox activations.

On the other hand, N-heterocyclic carbene (NHC)¹⁰-catalyzed redox reactions have been applied to the concise synthesis of esters^{11,12} and amides^{13,14} from aldehydes through the use of

internal or external redox protocols. In contrast, there have been fewer studies on NHC-catalyzed thioesterification. In fact, there have been only two previous reports to date, in which either cyclopropyl aldehyde^{11c} was used as a substrate or azobenzene¹⁵ was used as an oxidant for the internal or external redox reaction (Scheme 1). However, each reaction has its own limitations in terms of substrate scope or the formation of side-products. In particular, the choice of an appropriate external oxidant is the key to success in external redox thioesterification. In this paper, we describe a new efficient and practical method for the one-step conversion of aldehyde into the corresponding thioesters using phenazine as an external oxidant.

Table 1 Screening of Oxidants^a



Entry	Oxidant	Yield of 4a (%) ^b	Yield of 5 (%) ^b
1	MnO ₂ ^c	21	70
2	3a	59	27
3 ^d	3b , O ₂	67	23
4	DEAD	trace	88
5	IBX ^e	10	82
6	PhI(OAc) ₂ ^e	trace	90
7 ^f	3c	94	trace
8	3d	6	33

^a Conditions: **1a** (0.3 mmol), **2a** (1.1 equiv), oxidant (1.2 equiv), **A** (10 mol%), NEt₃ (10 mol%), THF (0.5 M), Ar, rt. ^b Isolated yields. ^c 5.0 equiv of MnO₂ was used. ^d Conditions: **1a** (2.0 equiv), **2a** (0.3 mmol), **3b** (10 mol%), **A** (10 mol%), NEt₃ (50 mol%), CHCl₃, MS4A, O₂, rt. ^e 2.0 equiv of oxidant was used. ^f Run for 6 h.

As a model reaction for thioesterification, we examined the reaction of benzaldehyde **1a** and phenylmethanethiol **2a** with catalyst **A** (10 mol%) and triethylamine (10 mol%) in the presence

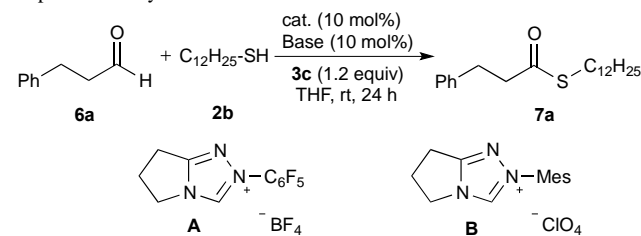
Table 2 Thioesterification of Aromatic Aldehydes^a

$\text{Ar}^1-\text{CHO} + \text{R}^2-\text{SH} \xrightarrow[\text{NEt}_3 (10 \text{ mol\%})]{\text{cat. A (10 mol\%)}, \text{3c (1.2 equiv)}, \text{THF, rt, 6 h}} \text{Ar}^1-\text{C(=O)}-\text{S}-\text{R}^2$			
Entry	Ar ¹	R ²	Yield of 4 (%) ^b
1	4-MeC ₆ H ₄	Bn	98 (4b)
2	4-MeOC ₆ H ₄	Bn	84 (4c)
3 ^d	4-ClC ₆ H ₄	Bn	90 (4d)
4	3-ClC ₆ H ₄	Bn	>99 (4e)
5	2-ClC ₆ H ₄	Bn	92 (4f)
6	4-NO ₂ C ₆ H ₄	Bn	83 (4g)
7 ^f	4-MeOCOC ₆ H ₄	Bn	91 (4h)
8	2-furyl	Bn	>99 (4i)
9	3-pyridyl	Bn	68 (4j)
10	Ph	(2-furyl)methyl	88 (4k)
11	Ph	<i>c</i> -hexyl	82 (4l)
12	Ph	^t Bu	72 (4m)
13 ^c	Ph	Ph	67 (4n)
14 ^c	Ph	4-MeOC ₆ H ₄	62 (4o)
15 ^c	Ph	4-FC ₆ H ₄	57 (4p)

^a Conditions: **1** (0.3 mmol), **2** (1.1 equiv), **3c** (1.2 equiv), **A** (10 mol%), NEt₃ (10 mol%), THF (0.5 M), Ar, rt. ^b Isolated yields. ^c 1.5 equiv of **2** and **3c**, 24 h.

of several oxidants (Table 1). The use of oxidants such as MnO₂,^{12d,e} quinone **3a**,^{12c,16} and riboflavin **3b**,¹⁷ which were used for NHC-catalyzed esterification, gave thioester **4a** in low to moderate yields due to the formation of disulfide **5** (entries 1-3). Other oxidants such as diethyl azodicarboxylate (DEAD), o-iodoxybenzoic acid (IBX)¹⁸ and PhI(OAc)₂ gave disulfide **5** as the major product along with a trace amount of **4a** (entries 4-6). We then examined heterocyclic compounds **3c** and **3d** as hydrogen acceptors (entries 7 and 8). To our delight, phenazine **3c** was shown to be a sufficiently mild oxidant to afford the desired product **4a** in high yield without the formation of any disulfide.

Table 3 Screening of Reaction Conditions for Thioesterification of Aliphatic Aldehyde^a



Entry	Catalyst	Base	Time (h)	Yield of 7a (%) ^b
1	A	Et ₃ N	24	55
2	A	DBU	24	71
3	B	Et ₃ N	24	trace
4	B	DBU	12	74
5 ^c	B	DBU	12	86

^a Conditions: **6a** (0.3 mmol), **2b** (1.1 equiv), **3c** (1.2 equiv), catalyst **A** or **B** (10 mol%), Base (10 mol%), THF (0.5 M), rt. ^b Isolated yields. ^c 1.5 equiv. of **2b** and **3c** were used.

After establishing the optimized reaction conditions, we

investigated the generality of this thioesterification (Table 2). A wide range of aryl and heteroaryl aldehydes bearing electron-donating and electron-withdrawing groups could be used regardless of their substituted position, to give the corresponding thioesters **4b-j** in good to high yields (entries 1-9). With regard to the thiol used, both alkyl and aryl thiols were tolerated under these conditions, while products **4n-p** were obtained in slightly lower yields even with 1.5 equiv of both thiols and **3c** in the case of aryl thiols (entries 10-15).

Table 4 Thioesterification of Aliphatic Aldehydes^a

$\text{R}^1-\text{CHO} + \text{R}^2-\text{SH} \xrightarrow[\text{THF, rt, 12 h}]{\text{cat. B (10 mol\%)}, \text{DBU (10 mol\%)}, \text{3c (1.5 equiv)}} \text{R}^1-\text{C(=O)}-\text{S}-\text{R}^2$			
Entry	R ¹	R ²	Yield (%) ^b
1		C ₁₂ H ₂₅	83 (7b)
2	BnO-	Bn	71 (7c)
3	<i>c</i> -hexyl	C ₁₂ H ₂₅	96 (7d)
4		C ₁₂ H ₂₅	80 (7e)
5		Bn	79 (7f) ^c
6		^t Bu	71 (7g) ^d
7		^t Bu	83 (7h)
8	PhCH ₂ CH ₂ -	Bn	91 (7i)
9	PhCH ₂ CH ₂ -	(2-furyl)methyl	81 (7j)
10	PhCH ₂ CH ₂ -	<i>c</i> -hexyl	88 (7k)
11	PhCH ₂ CH ₂ -	^t Bu	63 (7l)
12 ^e	PhCH ₂ CH ₂ -	4-MeOC ₆ H ₄	60 (7m)

^a Conditions: **6** (0.3 mmol), **2** (1.5 equiv), **3c** (1.5 equiv), **B** (10 mol%), DBU (10 mol%), THF (0.5 M), Ar, rt. ^b Isolated yields. ^c Racemic product was obtained. ^d *S-tert*-butyl 3-(*tert*-butylthio)-2-methyl-phenylpropane-thiolate was formed in 11% yield. ^e Run for 24 h.

We next explored the thioesterification of aliphatic aldehydes (Table 3). When the reaction of 3-phenylpropionaldehyde **6a** with an odorless dodecanethiol **2b** was carried out under the same reaction conditions, the yield of **7a** significantly decreased (entry

1). This could probably be attributed to the sluggish reaction due to the low reactivity of the aliphatic aldehyde. The use of DBU instead of Et₃N improved the chemical yield from 55 to 71% (entry 2). Replacement of the NHC precatalyst **A** by more nucleophilic *N*-mesityl triazolium salt **B**, along with an increase in the amounts of the thiol and base, led to a further increase in yield, and gave the thioester **7a** in 86% yield (entries 3-5).

We finally applied the optimal reaction conditions to a variety of aliphatic aldehydes (Table 4). Primary and secondary alkyl aldehydes bearing functional groups such as an isolated olefin, ether, and carbamate were converted into the corresponding thioesters **7b-f** in good yields without any problems (entries 1-5). The reaction of chiral α -amino aldehyde derivative **6f** was accompanied by racemization to provide the racemic thioester **7f** in 79% yield. Although α,β -unsaturated aldehyde **6g** underwent a redox reaction to give thioester **7g** as a major product together with the Michael adduct in 11% yield, β,β -disubstituted unsaturated aldehyde **6h** only gave the desired product **7h** in 83% yield (entries 6 and 7). In a similar manner, several alkyl and aryl thiols could be introduced to 3-phenylpropionaldehyde **6a** in good yields (entries 8-12).

In summary, we found that phenazine was the best oxidant for the NHC-catalyzed direct thioesterification of aldehydes, and did not lead to the formation of any disulfides. Furthermore, the appropriate combination of a NHC precatalyst and base (catalyst **A**/Et₃N, catalyst **B**/DBU) was shown to be important for the efficient thioesterification of aromatic and aliphatic aldehydes by redox activation.

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

^a Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto, 606-8501, Japan. Fax: +81-75-753-4528; Tel: +81-75-753-4569; E-mail: takemoto@pharm.kyoto-u.ac.jp

† This article is part of the joint ChemComm–Organic & Biomolecular Chemistry 'Organocatalysis' web-theme issue.

‡ Electronic Supplementary Information (ESI) available. For ESI see DOI: 10.1039/b000000x

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